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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
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ART UNIT	PAPER NUMBER
1634	18

DATE MAILED: 03/15/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/398,522	ISSA, JEAN-PIERRE	
	Examiner	Art Unit	
	Jeanine Goldberg	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10 and 13-32* is/are pending in the application.

4a) Of the above claim(s) *1-9 and 25-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 13-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

1. This action is in response to the papers filed January 28, 2002. Currently, claims 1-10, 13-32 are pending. Claims 1-9, 25-32 have been withdrawn from consideration as drawn to non-elected claims

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

4. This action contains new grounds of rejection necessitated by amendment.

Response to Declaration filed under 1.131

5. The declaration filed under 1.131 appears to a Katz-type declaration which is establishing each of the authors of Toyota et al (Cancer Research, Vol. 59, pg 4535-4541, September 15, 1999) contributed to the research effort that led to the article but did not contribute to conception of the invention as described in the present application. It appears that the declaration would have been more appropriately filed under 1.132 (see MPEP 715.01(c)), the examiner has considered the substance of the declaration as a 1.132 declaration such that the 102(a) rejection has been overcome.

Claim Objections

6. Claim 13 appears to have been incorporated into the independent claim 11. Therefore, Claim 13 does not appear to further limit claim 11. This may be easily overcome by deleting Claim 13.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 10, 13-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are broadly drawn to a method for detecting cellular proliferative disorder in a subject by contacting a nucleic acid containing specimen from the subject with an agent that provides a determination of the methylation state of APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1, SDC4 and CACNA1G gene such that a cellular proliferative disorder may be detected by detection of hypermethylation.

The specification teaches that aberrant methylation of CGIs have been detected in genetic disease such as the fragile-X syndrome, in aging cells and in neoplasia (pg. 3, lines 21-23). The specification teaches CpG-rich regions from APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 which are hypermethylated (pg. 7, lines 10-11, Figures 4A-4F). Table 5 of the specification states that the genes are "differentially methylated in disease versus normal tissue" (page 39). Further, Figure 4 illustrates the CpG islands for each of these genes. The specification

teaches that methylation analysis of CACNA1G was performed (pg. 24). The specification teaches that certain regions of CACNA1G are differentially methylated between tissue types. For example, regions 1 and 2 are not methylated in gliomas, region 3 is not methylated, 5,6 and 7 are more or an all or none methylation situation and regions 4 and 8 are part in breast/colon cell lines.

The art teaches that tissues are both hyper and hypo methylated as indicative of cancerous tissue. Balyin et al. (herein referred to as Balyin-1) teaches alterations in DNA methylation as a fundamental aspect of neoplasia (Advances in Cancer Research, Vol. 72, pg. 141-196, 1998). Baylin-1 discusses not only hypermethylation as associated with cancer, but additionally teaches that hypomethylation is associated with cancer. In the discussion, Baylin-1 teaches that in a number of models of carcinogenesis decrease in numbers of methyl groups appear to begin early in tumor progression and before the appearance of frank tumor formation (pg. 151). Baylin teaches that there is a clear association of DNA hypomethylation with tumors, however, the exact ramifications of this change for steps in tumor progression are poorly understood (pg. 151). Hypomethylation patters have been described for oncogenes in tumors. Baylin also teaches hypermethylation in cancer (pg. 152). Baylin provides several examples of CpG island hypermethylation associated with transcriptional inactivation of specific genes in neoplastic cells including Rb, VHL, p16, p15, E-cadherin, hMLH1, and ER (Table 2). Further, Nelson et al. (herein referred to as Nelson) teaches a method for detecting proliferative disorder associated with glutathione-S-transferase (GSTP1) which detect hypermethylation of GSTP1 promoter

in a tissue sample (abstract). As seen in Figure 5, hypermethylation does not appear to occur in normal tissues. Nelson teaches that a hypermethylated promoter for the human GSTP1 positively correlates with prostatic carcinogenesis (col. 3, lines 5-10). In a distinct article, Baylin et al. (herein referred to as Baylin-2) teaches that HIC-1 is within a CpG island which is abnormally methylated in many different types of tumors. Baylin-1 teaches hypermethylation of HIC-1 was analyzed in primary tumors and cultured cells lines (col. 22, lines 36-40).

Moreover, the art teaches analysis of CACNA1G, PITX2, GPR37 and SDC4 with respect to acute myeloid leukemia (Toyota et al. Blood, Vol 97, No.9, pages 2823-2829). Toyota specifically illustrates that normal bone marrow was analyzed and no significant methylation (2% of greater) was observed in any of the genes analyzed (page 2825, col 2). Toyota also provides distribution of methylation densities for CpG islands of 15 selected genes among 36 acute myeloid leukemia patients (page 2826). The table 2 illustrates the frequency of the methylation density of SDC4, GPR37 and PITX2 as frequently above 10% methylation. The table also clearly illustrates that approximately 92% of the patients had below 2% methylation density, which was indicated as not significant. Therefore, CACNA1G does not appear to be methylated significantly among AML patients.

Neither the specification nor the art teach the skilled artisan how to use the invention as broadly as claimed. First, the specification does not provide enabling disclosure directed to detecting hypermethylation of any CpG island within the genes as indicative of cellular proliferative disorder. The specification has identified very specific

CpG islands within the genes for hypermethylation. The specification does not appear to illustrate that any CpG island within the gene is associated with cellular proliferative disorders. It is unpredictable which CpG islands are differentially methylated and which CpG islands do not show any correlation with cellular proliferative disorders. Therefore, undue experimentation would be required to assess whether additional CpG island methylation allows for detection of cellular proliferative disorders. As seen in the example directed to CACNA1G, the specifically illustrates that certain CpG islands do not have methylation and are not associated with cellular proliferative disorder, for example region 3 (page 25). It is unpredictable which CpG islands are associated with cellular proliferative disorders.

Secondly, the specification illustrates generically that different genes are found to be differentially methylated in differed tissues. It is unpredictable that each and every gene is differentially methylated in every tissue encompassed by nucleic acid containing specimen. As provided within the instant specification, regions 1 and 2 were not methylated in gliomas (page 25). Thus, the specification illustreates that absent undue experimentation, it is unpredictable which CpG islands are associated with various tissues.

Moreover, cellular proliferative disorder very broadly defined in the specification such that it is unpredictable that the genes claimed would have any relationship to some of the diseases. Cellular proliferative disorders has been defined broadly in the specification to include, but are not limited to, low grade astrocytoma, anaplastic astrocytoma, glioblastoma, medulloblastoma, gastric cancer, colorectal cancer,

colorectal adenoma, acute myelogenous leukemia, lung cancer, renal cancer, leukemia, breast cancer, prostate cancer, endometrial cancer and neuroblastoma (pabe 30, lines 22-26). The specification has not broadly enabled the detection of each of these cellular proliferative disorders with a representative number of CpG islands such that the skilled artisan would clearly recognize the broad applicability to each of the disorders. Furthermore, Table 5 appears to indicate that not all genes are associated with each and every disease. Certain genes which are hypermethylated are specific to certain disorders. Similarly, the art appears to support that hypermethylation in AML varies among genes.

The specification has not provided any correlation between tumor and normal tissue regarding hypermethylation for APOB, CDX2, EGFR, FBN1, GPR37, HSPA6, IQGAP2, KL, PAR2, PITX2, PTCH, SDC1 or SDC4 such that the skilled artisan would be able to take the information and detect cellular proliferative disorders. It would be unpredictable to what degree these specific genes are infact differentially methylated in cancerous tissue and normal tissue. And it would require undue experimentation for the skilled artisan to perform the necessary experimentation to determine whether the listed genes are only hypermethylated in specific tumors and other cellular proliferative disorders such that cellular proliferative disorder may be detected. The skilled artisan would be required to sample tumor and normal cells from a clinical study to ascertain whether the tumors are hypermethylated and then determine whether this is only observed in tumors. Genes are known to be methylated at certain stages, however, mere methylation is not necessarily indicative of cellular proliferative disorders. Absent

showing that these genes are in fact differentially methylated in tumors and normal tissue, the skilled artisan would be unable to practice the claimed invention without undue experimentation. The specification does not appear to provide whether the samples were studied in all tumors, namely common tumors, leukemias, breast, prostate, and colon tumors, however were only hypermethylated in certain tissues and not in other tissues. The claims are not limited to the CpG islands which the specification has shown in Figure 4, but rather the gene as a whole or associated regulatory regions of the gene.

No information regarding the number of normal samples which were compared with the tumor samples. The specification has not provided any showings that a representative number or statistically significant number of the genes showed aberrant methylation such that cellular proliferative disorder would be indicated. It is unclear whether one sample was studied which had hypermethylation or whether a representative sample was reviewed to provide a representative analysis of the hypermethlyation of tumors. Moreover, from Table 5 it is unclear whether the tumor samples were from patients, were cell lines or of other origin. Additionally, within Table 5, the specification cites that the genes were hypermethylated in "common tumors" however, it is unclear what "common tumors" encompass and what common tumors do not encompass.

Conclusion

8. No claims allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of formal matters can be directed to the patent analyst, Chantae Dessau, whose telephone number is (703) 605-1237.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Goldberg
March 12, 2002

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600